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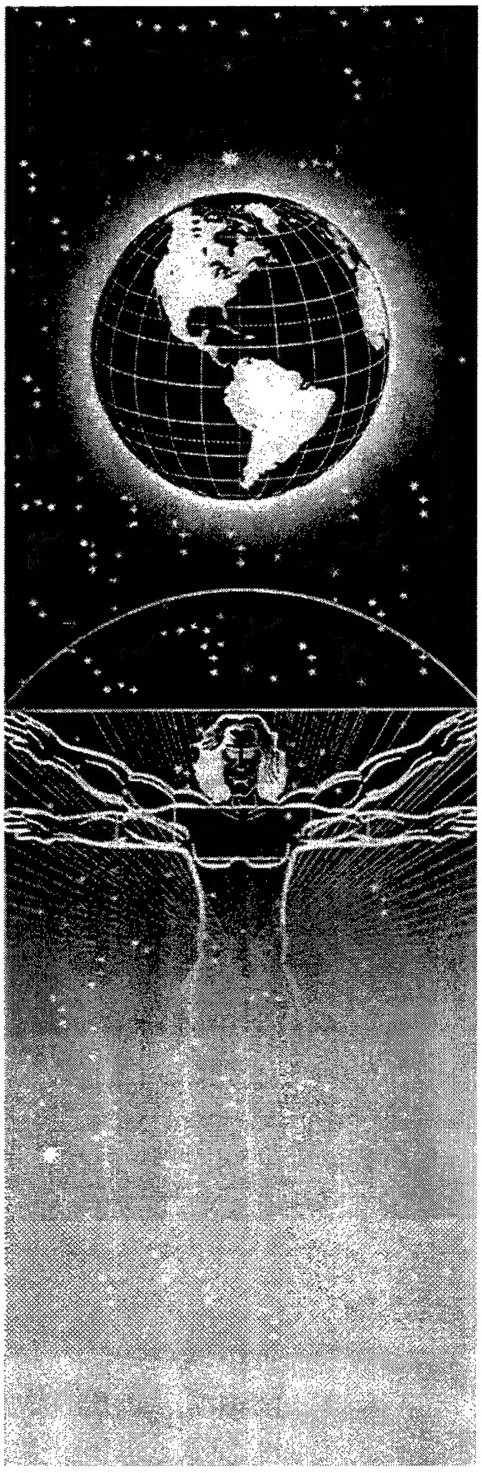

UNITED STATES AIR FORCE
ARMSTRONG LABORATORY

DERMAL ABSORPTION OF MODULAR ARTILLERY CHARGE (XM232)

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TECHNICAL REVIEW AND APPROVAL

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The animal use described in this study was conducted in accordance with the principles stated in the "Guide for the Care and Use of Laboratory Animals", National Research Council, 1996, and the Animal Welfare Act of 1966, as amended.

This report has been reviewed by the Office of Public Affairs (PA) and is releasable to the National Technical Information Service (NTIS). At NTIS, it will be available to the general public, including foreign nations.

This technical report has been reviewed and is approved for publication.

FOR THE DIRECTOR

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Soldiers handling Howitzer cartridges may have the potential to absorb the components of solid propellants through the skin of the hands. The purpose of this research was to determine if systemic absorption of chemical components of the new Modular Artillery Charge System (MACS) might be a hazard in operational military environments. We sampled the surfaces of solid propellant cartridges (XM232), which were stored under extreme environmental conditions, to determine the concentrations of various propellant components (nitroglycerine, diphenylamine, nitroguanidine, and nitrocellulose). After eleven months of storage, the only propellants found on the surface of the cartridges were very small quantities of nitroglycerin and diphenylamine. We used excised rat skin in static diffusion cells to investigate the dermal absorption of these components from the MACS in powdered form. Measured surface concentrations after storage and measured fluxes from diffusion studies were used to estimate systemic absorption in human exposure scenarios. Systemic absorption via the dermal route was compared with the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs ™) for these chemicals. Our results suggest that these propellant components are not absorbed sufficiently to be a systemic hazard under anticipated use conditions.

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PREFACE

This is the first of two technical reports assessing the absorption of chemical components of field artillery propelling charges through skin in order to provide information which is useful for assessing the potential hazards of soldier's exposures to Modular Artillery Charge System (MACS). This report suggests that the chemical components of the MACS high zone increment, called XM232, should not be hazardous to the health of soldiers because of dermal absorption. Part of the information presented in this report was presented at the 1997 JANNAF Propellant Development & Characterization Subcommittee and Safety & Environmental Protection Subcommittee Joint Meeting at NASA Ames Research Center, Sunnyvale CA on 17-21 March 1997. The analytical methods developed for this project were presented at the 1997 American Chemical Society Annual Meeting, San Francisco CA on 13-17 April 1997. Part of the funding for this project was provided by the Product Manager for Crusader Munitions, Picatinny Arsenal, NJ.

The animal use described in this study was conducted in accordance with the principles stated in the "Guide for the Care and Use of Laboratory Animals", National Research Council, 1996, and the Animal Welfare Act of 1966, as amended.

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INTRODUCTION

Potential health hazards of new Army weapon systems are of concern to health and safety professionals, the general public and weapon system developers. One concern is the potential for dermal absorption of materials and chemicals which soldiers may handle. Increments (XM231 & XM232), part of the Modular Artillery Charge System (MACS), are new components that need health and safety impact evaluations. These increments are fairly complex devices containing up to a dozen chemical components, including nitroglycerin, diphenylamine, nitroguanidine, and nitrocellulose. The systemic toxicity of MACS (XM232) in female rats was recently investigated (Kinkead et al. 1995 & 1996). After 28 days of being fed 2g propellant per kilogram of rat, the only effects were Methemoglobin elevation. There were no effects on body weight, organ weight, or reproductive parameters. Dermal absorption measurements are required to be able to determine if continued dermal contact with the propellants and combustible cases might be a systemic hazard. The purpose of this effort was to use fluxes from laboratory studies with excised rodent skin and measurements of XM232 chemical concentrations on the surface of the combustible cases to estimate the potential dermal absorption hazard to soldiers.

Propellants

The XM232 increment is the high zone propelling charge that will replace current 155mm M4A2, M119A1, and M203A1 propelling charges. The increment consists of a coated nitrocellulose-base3d combustible case, M30A1 propellant, and ignition system containing black powder and ball powder, and several additives to reduce cannon wear, flash, blast overpressure, and coppering. Range is adjusted by the number of increments (three to six) which are placed behind the projectile in the Howitzer. Chemical substances of concern are those comprising the rigid combustible case, the propellant, and combustion product residues which remain on the gun surfaces after firing (Army Environmental Hygiene Agency, 1994).

Primary components of the propellant (M30A1) are nitroguanidine, (47.7%); nitrocellulose, (28%); nitroglycerin, (22.5%); Ethyl Centralite, (1.5%); potassium sulfate, (1%); Cryolite, (0.3%); and graphite, (0.2%); (Hercules MSDS, 1992). Primary components of the combustible case are Nitrocellulose, (72%); Kraft fiber, (17%); Resin & additives, (10%); diphenylamine, (1%) and others (4%). Nitroguanidine is not a reproductive toxin and does not affect fertility (Coppes, et al., 1990). Nitrocellulose has very little toxicity information available and is assumed to be minimally toxic. No information is available about absorption through the skin. Nitroglycerin, which has been studied from many different types of vehicles is used therapeutically in transdermal delivery devices for angina, so it obviously can be formulated to penetrate the skin.

The ACGIH has only determined TLVs™ for nitroglycerin (0.46 mg/m^3), diphenylamine (10 mg/m^3) and graphite (2 mg/m^3) (ACGIH, 1996). Nitroglycerin also has a skin notation which means that there is a "potential significant contribution to the overall exposure by the dermal route".

Surface Sampling

The surfaces of twelve XM232 Modular Artillery Charge System increments were sampled at Yuma Proving Ground in May 1997 after being stored outside in metal ammunition cans for eleven months. These cans were exposed to the extreme temperature fluctuations which are normal in the desert during a year (30 to 119 degrees F and 10 to 100% relative humidity). The exterior surface of the increment was sampled by carefully wiping one quarter of the cylindrical surface (280 cm^2) with a dry gauze pad. Samples were transferred to capped centrifuge tubes and carried back to Wright-Patterson AFB for analysis by High Performance Liquid Chromatography (HPLC) with ultraviolet detection. These wipe samples were analyzed for nitroglycerin, diphenylamine,

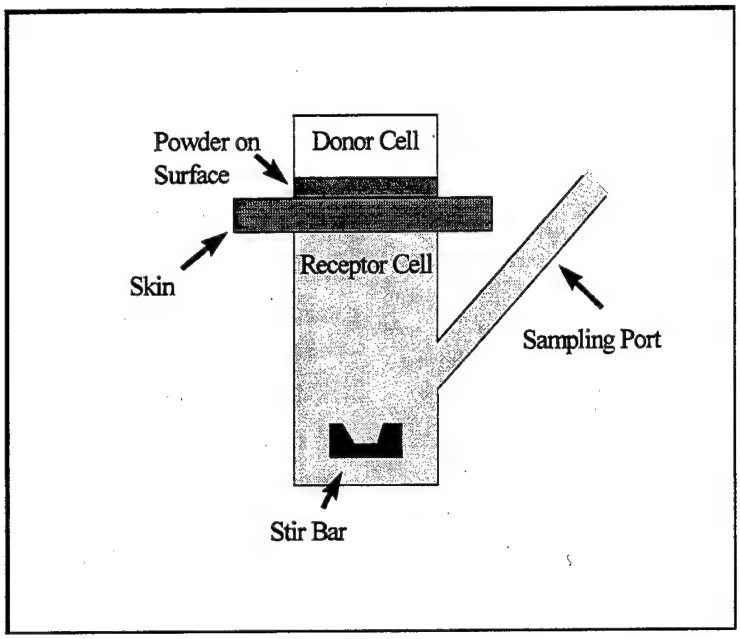

Figure 1. Schematic of a Static Diffusion Cell used for Flux Measurements

nitroguanidine, nitrocellulose, dibutylphthalate, and 4-aminobiphenyl (a potential contaminant of diphenylamine).

Static Diffusion Cell Studies

In *in vitro* experiments, we used static diffusion cells to measure the flux of chemical across excised WF/PmWp-fz rat skin. Female WF/PmWp-fz rats (246 - 290 grams) were euthanized with CO_2, and a circle the size of the diffusion cell flange was marked on the back with indelible ink. The skin on the back was excised and cleaned of hypodermis by scrapping with a razor blade. The outer surface of the excised skin was placed between a donor and receptor cell and clamped in place. Figure 1 shows a schematic depiction of the diffusion cell. The receptor cell was surrounded by a water jacket through which 37°C water circulated. Powder was placed on the outer surface of the skin and the appearance of chemicals in the receptor solution (0.9% saline) was determined over time, by taking 60 μL samples of the receptor solution. The receptor solution was well-stirred and we took care to keep air out of the system so that the skin was in complete contact with the receptor solution. Concentrations of nitroglycerin, diphenylamine, nitroguanidine and nitrocellulose were analyzed using HPLC.

the surface wipes. A Hewlett Packard HPLC with a 220 x 4.6 mm RP-18 column was used. Carrier fluid consisted of 68% methanol and 32% water. Flow rate was 0.4 mL/min. Injection volume was 10 µL. These compounds were stable in both matrices for 72 hours. The presence of trace components was confirmed independently by gas chromatography/mass spectrometry and supercritical fluid chromatography (Tsui et al., 1997).

Nitrocellulose was analyzed by ion chromatography after hydrolysis with sodium hydroxide. The nitrocellulose containing solution was vacuum filtered through an inorganic, 0.02 µm, membrane filter (Whatman, anodisk 47). The filter was washed with methanol to remove interfering nitrate esters and then soaked in acetone for 15 minutes to dissolve the nitrocellulose. The acetone solution was evaporated under a stream of nitrogen and then hydrolyzed with NaOH at 100 °C for 30 minutes. Nitrocellulose concentration was calculated as the mass of nitrogen found as nitrate and nitrite after ion chromatography.

Flux and Skin Absorption Time

Flux was determined from the slope of the cumulative mass versus time plot, and traditionally has units of mass/(area x time). The factors which impact steady-state flux are illustrated in a version of Fick's Law (Scheuplein & Blank, 1971):

$$Flux = \frac{K_m D}{\delta}(C_{out} - C_{in}) \qquad (1)$$

where K_m is the membrane/chemical partition coefficient; D is diffusivity (length^2/time); δ is thickness (length) of the membrane; C_{out} is concentration (mass/length^3) outside the membrane; and C_{in} is concentration inside the membrane.

"Skin absorption time" is a new method to relate potential dermal exposures to existing guidelines such as the ACGIH Threshold Limit Values (TLVs™) or OSHA's Permissible Exposure Level (PEL) (Walker et al., 1996). This method has been developed for pure liquids or liquid solutions, but modified here, for powders or solids. It requires absorption rate information and provides quantitative information that is both intuitive and useful in a case such as this. It is a two step process: First, an estimate of the total amount of chemical which would be inhaled at the occupational limit value is calculated:

$$TA = EL \times RR \times T \qquad (2)$$

where;

TA is total chemical absorbed (mg),

EL is the exposure limit (mg/m^3),
RR is the appropriate respiratory rate (m^3/hr), and
T is the shift time (hr).

Then the time required to get this amount of chemical through the skin is calculated:

$$SAT = \left(\frac{TA}{MSD \times k \times A} \right) \quad (3)$$

Where

SAT is skin absorption time (hr),
MSD is the mass/surface density of the chemical on the skin (mg/cm^2),
k is a first order rate (hr^{-1}) related to flux, and
A is surface area of skin exposed (cm^2).

The denominator of Equation 3, which calculated the total absorbed from the skin route, is novel but intuitive. Amount of chemical diffusing across the skin is proportional to the concentration difference across the skin, according to Equation 1. Mass/surface density can be used as a surrogate for concentration, since concentration of a powder is hard to define. A change in mass/surface density should also affect chemical absorption proportionally just like a change in concentration. When the amount of chemical per surface area on the skin is continually increased, amount diffusing across the skin would increase only up to a point. Past this point a further increase in mass on the skin causes no increase in flux; but below this point increasing mass/surface density would cause a proportional increase in amount of chemical absorbed. In this regime, flux can be expressed as a pseudo first order process, units of hr^{-1}, during the time before there is excess on the skin, analogous to the situation with concentration. Our experiments were done with excess M30A1 on the skin (approximately 500 mg/4.9 cm^2) and therefore the rate that was calculated would be the maximum rate possible. When there is not a large excess of M30A1 on the surface, i.e. actual exposure situation, the flux would be significantly reduced. The surface area exposed affects the amount of chemical which penetrates proportionally, i.e., doubling the surface area doubles absorption if the other parameters stay the same. Equations 2 and 3 make several assumptions:

1. the flux is constant throughout the whole exposure;
2. the mass of chemical on the skin is equivalent to the amount of chemical on the surface in contact with the hands; and
3. the mass of chemical on the exposed skin surface is constant (i.e., not diminished by absorption or accumulated by repeated contact).

Because of the assumptions and potential variability in this time calculation it should not be interpreted to be a quantitative answer. The resultant SAT gives a categorical idea of whether it takes minutes, hours, or days to get the same body burden as one would get from being exposed to the limit value for a whole work shift.

RESULTS AND DISCUSSION

Propellant on Increment Surfaces

Amount of constituent chemical components contained in the XM232 increment on the surface of increments is shown in Table 1. Only Nitroglycerin and diphenylamine were found on the surface of the combustible case. It is not known whether these concentrations are left over from the manufacturing process or due to diffusion from inside the combustible case through to the surface. Nitroglycerin has been shown to diffuse through the combustible case of another propelling charge (Manning, 1986). Diphenylamine was a minor component (1%) of the combustible case and was expected to be more available on the surface of the increment than nitroglycerin.

Table 1. Mass density of chemical components of XM232 increments found on the combustible surface with a gauze wipe.

Chemical	Mass recovered (μg ± S.D.)	Mass density (μg/cm^2)
Nitroglycerin	35.2 ± 16.6	0.127
Diphenylamine	7.99 ± 4.4	0.029

Using our methods we would have been able to detect the following amounts of chemical on the surface of the increments: 2.8 micrograms for nitrocellulose, 0.21 nanograms for nitroguanidine, 0.96 nanograms for nitroglycerin, 0.25 nanograms for diphenylamine, 0.48 nanograms for 4-aminobiphenyl, 1.62 nanograms for dibutylphthalate, and 0.99 to 4.38 nanograms for dinitrotoluenes. Standard curves for these chemicals were made up in the receptor solution.

We also used methanol soaked gauze to wipe a different quadrant of the same increments. Because methanol was a good solvent for these propellants the methanol soaked gauze removed up to ten times more nitroglycerin from the surfaces of the increments. It appeared that the methanol wipes may have been desorbing chemicals from inside the combustible cases instead of from the surface. Dry gauze was a much better surrogate to estimate transfer to soldier's hands.

surface. Dry gauze was a much better surrogate to estimate transfer to soldier's hands.

Dermal Absorption of Propellant Components in Rat Skin

We attempted to measure the absorption of nitrocellulose, nitroguanidine and nitroglycerin through excised rat skin in the static diffusion cell after placing powdered M30A1 propellant on the surface of the skin, as previously described. Only nitroglycerin could be detected in the saline receptor solution; the other chemicals did not penetrate sufficiently to be above the limit of detection. The results of a experiment showing diffusion of nitroglycerin in six static diffusion cells is shown in Figure 2.

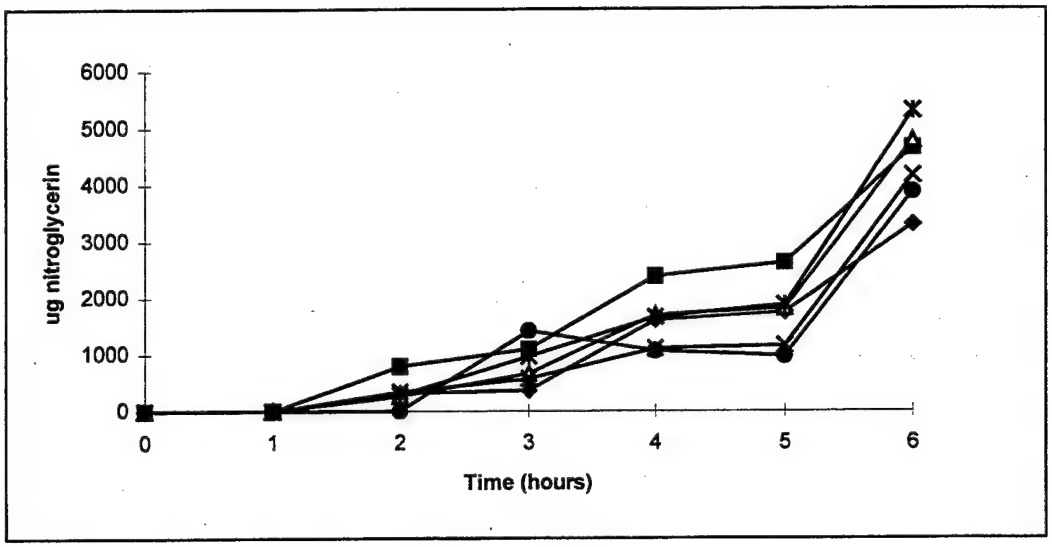

Figure 2. Plot of the cumulative amount of nitroglycerin absorbed through the excised skin of female WF/PmWp-fz rats.

The average nitroglycerin flux calculated from the slope of these plots was 0.03 mg/cm^2/hr. The slope of a natural log plot of this data gives a value of 0.584 hr^{-1}. No flux values could be determined for the other two chemicals because they couldn't be detected in the receptor solution, but based on the detection limits the flux for nitroguanidine and nitrocellulose must be three to five orders of magnitude less than the flux of nitroglycerin.

Skin Absorption Time for Nitroglycerin

Nitroglycerin has a fairly low TLV™ (0.46 mg/m^3) which when multiplied by OSHA's default respiratory rate for light work (10 m^3 for an 8 hour shift) gives an estimate of the total absorbed dose of 4.6 mg, if exposed to the TLV™ for an entire work shift (see Equation 2). Based on Equation 3 we can calculate the skin absorption time for nitroglycerin absorption from M30A1 propellant using the palm area of both hands (500cm^2):

With the measured amounts of nitroglycerin on the surface of the increment (.000127 mg/cm^2) and with the absorption rate determined in the laboratory (0.585 hr^{-1}), it would take 124 hours (5.2 full days or 15.5 eight-hour shifts) of constant absorption across the skin of both hands for a soldier to absorb what is considered by the ACGIH to be a "safe" amount of nitroglycerin every eight hours. Because there are only 24 hours in a day, a constant exposure to this amount of nitroglycerin on the increment surface, would result in an estimated maximum body burden (0.0371 mg/hr x 24 hrs = 0.89 mg) that would be about one-fifth of the amount absorbed at the ACGIH TLV™ (4.6 mg) for an eight-hour workshift.

These values assume that rat and human skin have the same permeability. Several studies have shown that rat skin is two to three times more permeable than human skin (Vecchia, 1997; McDougal, 1990). Our estimate of the amount absorbed would therefore err on the high side. This calculation also assumes that the health effects for which the TLV™ is protective are also the most important effects via the skin route. In the case of nitroglycerin there appear to be no route specific effects. Nitroglycerin affects smooth muscle structures, particularly in the vascular system, and the effects are severe headaches, dizziness, and postural weakness (Needleman & Johnson, 1980).

Dermal Absorption of Combustible Case Components in Rat Skin

Wipes from the combustible case were assayed for nitrocellulose and diphenylamine. Only diphenylamine, in extremely small amounts, was recovered from the surfaces of the combustible cases (Table 1) which were stored for eleven months. We attempted to measure the appearance of diphenylamine in the receptor solution during a six-hour exposure of isolated "Fuzzy" rat skin to pure diphenylamine powder on the skin surface, as previously described. No diphenylamine was detected in the receptor solution after six hours; therefore, a rate of absorption could not be calculated.

Although there is not enough information to calculate a "skin absorption time", some comparisons with the calculation for nitroglycerin (equation 4) can be made. The TLV™ for diphenylamine (10 mg/m^3) is more than twenty times higher than that for nitroglycerin (0.48 mg/m^3) and the diphenylamine concentration found on the surface is about one-fourth of the concentration of nitroglycerin which was found. Even if diphenylamine had the same absorption rate as nitroglycerin (it is obviously much less), it would take about 95 times longer (600 days) to absorb the safe amount (as estimated by the TLV™). There are only 24 hours in a day, so with a constant exposure to this amount of diphenylamine, it would be impossible to exceed the "safe" amount.

SUMMARY AND CONCLUSIONS

Developers of the new Modular Artillery Charge System need information about the dermal absorption of constituent chemical component residue from increments. With the Product Manager for Crusader Munitions at Picatinny Arsenal, we have developed a program to answer these questions. We measured mass of chemical constituents on the surface of XM232 increments stored for eleven months, determined the flux of chemical components from powdered propellant across rat skin in the laboratory, and combined this information to give a temporal relationship between dermal exposures and acceptable inhalation exposure levels.

Of the five primary chemical components measured on the surface of XM232 increments stored for eleven months, only nitroglycerin and diphenylamine could be detected. All amounts on the surface were extremely low. It is not known for sure whether these chemicals were left on the surface during the manufacturing process, or whether they have diffused through the combustible case. It is most likely that they have diffused through the casing since nitroguanidine (which is present in the propellant at about twice the concentration of nitroglycerin) was not found on the surface. All components of the propellant would be found on the surface if a residue was left during manufacturing.

When powdered M301 propellant was placed on rat skin in a standard diffusion cell in the laboratory only nitroglycerin was found in the receptor solution. The nitroglycerin component of MACS penetrates rat skin at an extremely low rate. The nitroglycerin in transdermal drug delivery systems is made to transfer more rapidly by proprietary formulations which enhance penetration. The other two major components of MACS, nitrocellulose and nitroguanidine, did not penetrate enough to be measured. Based on the good detection limit which we achieved for these chemicals, these chemicals can be ruled out as a systemic hazard from dermal absorption.

When pure diphenylamine was placed on rat skin in the diffusion cell, to simulate absorption from the surface of the combustible case, no diphenylamine could be found in the receptor solution. Based on the good detection limit and comparison with nitroglycerin, diphenylamine can be ruled out as a systemic hazard from dermal absorption.

In conclusion, systemic absorption through the skin of the chemical components of XM232 MACS increments would probably not be a hazard in operational military environments. We found that in nearly a year of storage at very warm temperatures, only nitroglycerin (component of the propellant) and diphenylamine (component of the combustible case) could be found on the increment surface in any reasonable amounts. We also found that when rat skin

was exposed to the powdered propellant mixture, only nitroglycerin penetrated well enough to be detected. We expect that nitroglycerin would be the only potential hazard from the propellant. The estimated length of time to exceed the acceptable (according to the TLV™) body burden for nitroglycerin through the palmar surface of both hands, exposed to field artillery propelling charges such as these, would probably be much longer than an 8-hour work shift. Because the rate was so low, it was not possible to calculate an absorption rate for diphenylamine, a 1% component of the case. Based on our studies and calculations, it is extremely unlikely that XM232 would constitute toxicological hazard to soldiers by dermal absorption.

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